

## REMARKS

The Office Action has rejected Claims 15-19, 25, 26, 29 and 30 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. In addition, it has rejected Claims 15-22, 25, 26, 29 and 30 under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 4,224,326 to Matsumoto ("Matsumoto") in view of the teachings in WO 97/48397, to which Beidermann et al. are inventors ("Beidermann et al.").

Applicants are submitting the following comments which are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

In support of the rejection of Claims 15-19, 25, 26, 29 and 30 under 35 U.S.C. §112, first paragraph, the Office Action alleges that the specification fails to comply with the written description requirement. The Office Action alleges that terms, such as "aryl", "arylcarbonyl", "heteroaryl" and "heteroarylcarbonyl" used to define substituents in R<sup>3</sup> do not meet the written description requirement, since, according to the Office Action, they are not defined.

Contrary to the allegations in the Office Action, the present application does meet the written description requirement in accordance with the provisions of 35 U.S.C. §112, first paragraph.

As indicated in the Office Action the terms "aryl", "arylcarbonyl", "heteroaryl" and "heteroarylcarbonyl" are part of the definition of R<sup>3</sup>. However, contrary to the allegations in the Office Action, these terms are defined in the specification

With respect to the term "aryl", attention is directed to Page 8, Line 10 to Page 9, Line 16 of the instant specification. As defined, "aryl" is an aromatic radical with 6 to 14 carbon atoms. The specification even provides some examples, such as phenyl, naphthyl, fluorenyl and phenanthryl. As defined, the aryl group may be unsubstituted or substituted and the substituents are defined. Thus, aryl is clearly defined in the specification.

The specification also defines the term "arylcarbonyl". Attention is directed to Page 9, Lines 17-31 of the instant specification. As defined, "arylcarbonyl" is an aryl group attached to a carbonyl. The specification gives examples, such as benzoyl, naphthoyl, fluorenroyl and phenanthroyl. Again, the aryl group may be unsubstituted or substituted with the substituents for aryl. Thus, "arylcarbonyl" is defined in the specification.

In addition, the specification also defines the term "heteroaryl". Attention is directed to Page 9, Line 32 to Page 10, Line 18 of the instant specification. As defined, "heteroaryl"

signifies an unsaturated heterocyclic radical and is mono-, bi- or tricyclic, preferably monocyclic, whereby, one or more, preferably one to four, especially one or two, most preferably one carbon atom(s) of a corresponding aryl radical are replaced by a hetero atom selected from the group consisting of nitrogen, oxygen and sulfur, whereby the binding ring has preferably 4 to 12, especially 5 to 7 ring atoms; whereby heteroaryl is unsubstituted or is substituted by one or more, especially 1 to 3, substituents selected independently from the group consisting of the above-mentioned substituents of aryl...

Id. Moreover, the specification provides several examples of heteroaryl. Thus, the term "heteroaryl" is adequately defined.

Finally, "heteroarylcarbonyl" is also defined in the specification. Attention is directed to Page 10, Lines 19-32 of the instant specification, wherein heteroarylcarbonyl is defined as heteroaryl, as defined in the specification, attached to a carbonyl group. Again, it provides several examples. Thus, heteroarylcarbonyl is adequately defined.

Inasmuch as the aforementioned terms are used, *inter alia*, in the definition of R<sup>3</sup>, it is quite apparent that these definitions are implicit in the use of these terms in R<sup>3</sup>. Thus, it is clear that in light of these definitions, contrary to the allegations of the Office Action, there is adequate guidelines in the specification to define these terms. Accordingly, it is respectfully submitted that the inventors had possession of these embodiments encompassed by the terms "aryl", "arylcarbonyl", "heteroaryl" and "heteroarylcarbonyl" when reference is made to R<sup>3</sup>. Thus, the specification adequately describes these terms in the specification.

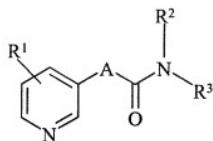
Further, it is respectfully submitted that the definition in R<sup>3</sup> was not broadened during prosecution and that the definition in R<sup>3</sup> is the same scope as defined in original Claim 5. Thus, the definition of R<sup>3</sup> is described in the original application, as filed. This again evidences that the inventors had possession of this subject matter at the time of the filing of the instant application.

Therefore, for the reasons provided, this rejection of the claimed subject matter under 35 U.S.C. §112, first paragraph, is obviated. Withdrawal thereof is respectfully requested.

In support of the rejection of Claims 15, 25, 26, 29 and 30 under 35 U.S.C. §103, the Office Action cites Matsumoto in view of Beidermann et al.

The present application is directed to, *inter alia*, a method of treating or preventing a disease or medical condition in a mammal selected from rheumatoid arthritis, inflammatory disorder, macular degeneration, psoriasis, retinopathy, preneoplastic lesions, and

hyperplasia, which method comprises administering to said mammal a compound of Formula I or a pharmaceutically acceptable salt thereof:



I

wherein:

A is selected from the group consisting of the group members C<sub>1-10</sub>-alkylene, C<sub>2-10</sub>-alkenylene, and C<sub>2-10</sub>-alkinylene, which group members may be optionally substituted by one, two or three groups independently selected from C<sub>1-3</sub>-alkyl, fluoro, chloro, and bromo;

R<sup>1</sup> is selected from hydrogen, C<sub>1-6</sub>-alkyl, fluoro, chloro, bromo, and perfluoro-C<sub>1-3</sub>-alkyl;

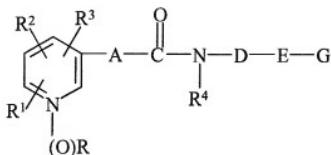
R<sup>2</sup> is selected from hydrogen, C<sub>1-6</sub>-alkyl, and C<sub>2-6</sub>-alkenyl; and

R<sup>3</sup> is selected from the group consisting of the group members C<sub>1-6</sub>-alkyl, (C<sub>5-8</sub>-cycloalkyl)-C<sub>1-6</sub>-alkyl, (C<sub>5-8</sub>-heterocyclyl)-C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl (C<sub>5-8</sub>-heterocyclyl)-C<sub>1-6</sub>-alkyl, and C<sub>1-5</sub>-alkylcarbonyl (C<sub>5-8</sub>-heterocyclyl)-C<sub>1-6</sub>-alkyl, which group members may be optionally substituted by one,

two or three groups independently selected from C<sub>1-6</sub>-alkyl, fluoro, chloro, bromo, oxo, perfluoro-C<sub>1-3</sub>-alkyl, aryl, arylcarbonyl, heteroaryl, heteroarylcarbonyl, C<sub>5-8</sub>-cycloalkyl and C<sub>5-8</sub>-heterocyclyl.

Matsumoto is directed to 2-aryl-1H-perimidines as immunosuppressant agents.

Beidermann et al. is directed to the use of pharmaceutically effective compounds of the formula



for the treatment of, *inter alia*, tumors or for immunosuppression.

The Office Action alleges that Matsumoto teaches that immunosuppressive agents are "used to treat or suppress mammalian immune response as a means of treating the autoimmune disease rheumatoid arthritis", referring to Claims 1 and 9. See Page 3 of Office Action. It also refers to Example 27, wherein it alleges that in Example 27, Matsumoto teaches rheumatoid arthritis is an inflammatory disorder where reduction of inflammation is a marker of immunosuppressive activity. The Office Action cites Beidermann et al., alleging that it discloses on Page 82, compound 259, a compound which it alleges falls within the scope of the present claims. It also alleges that Beidermann et al. disclose that this compound therein is also an immunosuppressant agent.

According to the Office Action, it would be obvious to use the compounds of the Beidermann et al. for treating rheumatoid arthritis because of the commonality of the compounds in both references having the utility of an immunosuppressant.

It is respectfully submitted that the Office Action has not made out a *prima facie* case of obviousness.

The Office Action refers to Claims 1 and 9 of Matsumoto for support of its proposition that immunosuppressants are useful for treating rheumatoid arthritis. However, Claims 1 and 9 in Matsumoto are only specific to the 2-aryl-1H-perimidines disclosed therein.

Claims 1 and 9 do not indicate that immunosuppressive agents can be used to treat rheumatoid arthritis. Based upon the specificity of the claimed subject matter recited in Claims 1 and 9, one of ordinary skill in the art can conclude that 2-aryl-1H-perimidines can be used to treat rheumatoid arthritis, but one of ordinary skill cannot make any generalization that immunosuppressant agents in general are also useful for treating rheumatoid arthritis. Further, Example 27 in Matsumoto discloses that 2-(p-trifluoromethylphenyl)-1H-perimidine hydrochloride was effective in inhibiting hind paw swelling resulting from adjuvant induced edema in rats, but again one of ordinary skill in the art cannot generalize. Again, the teachings therein are specific to the compounds of Matsumoto. As is well known in statistics, one cannot make a generalization from just one example. Thus, assuming, *pro arguendo*, that compound 259 in Beidermann et al. falls within the scope of the compounds utilized in the present application, even though compound 259 in Beidermann et al. is taught to be useful for immunosuppression, the Office Action fails to provide sufficient data points and/or evidence to make any generalizations regarding immunosuppressant activity and rheumatoid arthritis.

Before Applicants need to reply on the merits, the Office Action must provide enough evidence or provide sufficient basis to meet its burden and shift the burden to Applicants. Here, the Office Action has not met its burden based upon the utility of one class of compounds. The correlation is just too tenuous for it is based on only one example. Therefore, the Office Action has not shown that compound 259 can be used to treat rheumatoid arthritis. The Office Action has not met its burden and has not shifted it to the Applicants. Accordingly, the Office Action has not established a *prima facie* case of obviousness.

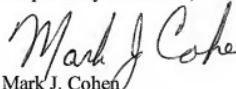
It is respectfully submitted that Claims 25, 27 and 30 are patentable for an additional reason. Applicant reiterates the comments hereinabove. But in addition, the Office

Action has not made out a *prima facie* case of obviousness with respect to this claimed subject matter for another reason. Matsumoto is being cited for the utility of an immunosuppressive agent being useful for the treatment of rheumatoid arthritis. Claims 25, 27 and 30 do not recite that compounds therein are useful for treating rheumatoid arthritis. They recite that the diseases for which the present method is being utilized are age-related macular degeneration, proliferative retinopathy, diabetic retinopathy, benign prostatic hyperplasia and venous neointimal hyperplasia. Thus, none of these claims recite rheumatoid arthritis. Therefore, assuming, *pro arguendo*, that compound 259 falls within the scope of Beidermann et al., it is respectfully submitted that the combination of art does not teach, disclose or suggest the utility described in the claims, as none of these diseases are rheumatoid arthritis.

Therefore, for the reasons provided, the rejection of the pending claims under 35 U.S.C. §103 is obviated. Withdrawal thereof is respectfully requested.

Thus, in view of the Remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully Submitted,

  
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